

REMARKS

Claims 49-64 are newly added. Support for these claims may be found, *inter alia*, on page 4, lines 14-19; page 6, lines 8-10; page 9, lines 13-14; and page 11, lines 13-17.

Claims 2-3, 17, 20, 42, 44 and 47 have been amended. Claims 1, 7, 9, 41, 43, 45-46 and 48 have been canceled without prejudice. With the entry of this amendment, claims 2-6, 11, 17-18, 20-22, 42, 44, 47 and 49-64 will be pending.

The §112 Rejections

The Examiner rejected claims 1-7, 9, 11, 17-18, 20-22 and 41-48 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 44-48 were also rejected under 35 U.S.C. 112, first paragraph, as being non-enabling.

During the telephonic interview, the Examiner indicated that at the core of the 112 rejections was the term "vitamin D moiety." She further indicated that Applicants could address the 112 rejections by adding structure to further define "vitamin D moiety." Accordingly, Applicants have added formula II to each of the independent claims, as requested by the Examiner during the interview. Support for this amendment can be found, *inter alia*, on page 11, lines 13-17. In addition, the Examiner also indicated during the interview that Applicants could obviate the 112 rejections by further defining the term "target molecule moiety." "Target molecule moiety" has been defined in varying scope in the independent claims and some of the new dependent claims. For example, Applicants have deleted "protein with bone mineral binding domains," "a steroid," and "an antibody", consistent with what the Examiner requested during the interview. The Examiner indicated that these 112 rejections would be withdrawn in view of such an amendment. Support for these amendments can be found, *inter alia*, on page 4, lines 14-19. Accordingly, Applicants respectfully request reconsideration and withdrawal of these §112 rejections.

Claims 41, 43 and 48 were also rejected under 35 U.S.C. §112, first paragraph, as containing new matter. These claims have been canceled without prejudice. This §112 rejection is, therefore, moot.

Claims 42 and 44-45 were also rejected under 35 U.S.C. §112, second paragraph, as being indefinite due to the recitation of "includes." Applicants have deleted "includes" from claims 42 and 44 and inserted "comprises" in its place. Claim 45 has been canceled without prejudice. Withdrawal of this §112 rejection is respectfully requested.

Accordingly, Applicants respectfully submit that all pending claims meet all the requirements of §112.

Prior Art Rejections

The Examiner also variously rejected the pending claims over certain prior art. Applicants respectfully traverse each of these art-based rejections, many of which, however, are now moot, and request reconsideration thereof. With entry of the above amendments, independent claims 20, 44 and 59 are pending. The other claims pending in the application have either been amended to depend from these independent claims, or have been added and now depend from these claims. Accordingly, Applicants will focus on the rejections to the independent claims, beginning with claim 44.

Independent Claim 44

The Examiner has rejected claim 44 under 35 U.S.C. 103(a) as being unpatentable over Kobayashi et al. (Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892) ("Kobayashi") or U.S. Patent No. 4,292,250 issued to DeLuca et al. ("DeLuca") each in view of Orme *et al.* (Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892) ("Orme") and U.S. Patent No. 4,661,294 issued to Holick ("Holick"). Applicants respectfully transverse the rejection and request reconsideration.

At the outset, Applicants respectfully submit that they were the first to discover and recognize that vitamin D compounds can be conjugated to certain molecules capable of directing the vitamin D to a tissue or organ specific site *in vivo*. The gravaman of the Examiner's rejections, however, appears to be that any molecule bonded to a vitamin D molecule anticipates applicants' claimed invention. Applicants certainly assert no argument that many molecules of many types may be bonded to vitamin D compounds. However, just because a vitamin D is bonded to another molecule does not mean the attached molecule can deliver the vitamin D to a tissue of interest. Nothing in the cited references, alone or in combination, suggests or discloses

that their disclosed species have the capacity to provide targeted, site-specific delivery of a vitamin D.

The primary reference Kobayashi discloses nothing more than a 1,25-(OH)₂ vitamin D₃ linked to a plasma protein, bovine serum albumin, for the purpose of eliciting an immunogenic response when injected into a species other than bovine. The purpose of such injection is to produce anti-1,25-(OH)₂D₃ antibodies. Nonetheless, the Examiner contends that the Kobayashi 1,25-(OH)₃D₃-BSA complex is a targeted delivery conjugate as recited in the claimed invention. Nowhere, on the record, is there any evidence showing BSA has a binding affinity for a specific tissue or organ such that it is capable of directing the 1,25-(OH)₂D₃ to such a site. The Kobayashi complex is nothing more than a convenient vehicle for raising anti-1,25-(OH)₂D₃ antibodies. The antibodies are subsequently used in an *in vitro* assay. Nothing in Kobayashi, alone or combined, reasonably suggests Applicants' claimed invention to the skilled artisan. Kobayashi shows no recognition of the problem addressed by applicants, and the skilled artisan would not have been likely to consider such reference in attempt to solve the problem.

Although Applicants maintain that the Kobayashi, alone or in combination, does not disclose or suggest Applicants' claimed invention, Applicants submit herewith the appended declaration under 37 C.F.R. §1.131 by inventors, Drs. Richard B. Mazess and Charles W. Bishop, ("the Declaration"), to antedate Kobayashi as prior art (the Declaration is submitted unexecuted; an executed copy will be submitted in the near future). While the Declaration is deemed self-explanatory, Applicants emphasize that inventors demonstrate that their invention was conceived of at least as early as September 1996, which is prior to the January 15, 1997, the printed publication date of Kobayashi, and prior to the actual publication date of January 23, 1997, the date received by subscribers (see Exhibit A attached hereto which verifies the actual publication date), and that Applicants diligently pursued a patent application for this invention from at least as early as September, 1996 to February 13, 1997, which is the priority date of the present patent application. As such, Applicants have demonstrated on the record their conception and diligence to the filing of the provisional patent application to which this application claims priority. In view of the Declaration, Applicants respectfully submit that Kobayashi does not constitute prior art to the present invention. Consequently, the art rejections using Kobayashi are moot.

Regarding the combination of De Luca, Orme and Holick, Applicants respectfully submit that a *prima facie* case of obviousness has not been established in view of the amendment to claim 44. To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As set forth in the previous response, Applicants maintain that the Examiner has mischaracterized the teachings of De Luca. More particularly, DeLuca does not teach or suggest, among other things, a conjugate comprising a target molecule moiety having an affinity for a tissue of interest. The gravamen of Examiner's rejection appears to be that glucuronide is a target molecule moiety, and that glucuronide has an affinity for plasma. While DeLuca may disclose "new 25-hydroxy vitamin D₂ 25-glucuronide derivatives among which is 25-hydroxy vitamin D₂-25-D-glucuronic acid," a careful review of DeLuca shows that it does not teach or suggest that glucuronide is a "target molecule moiety" or can be used as a "target molecule moiety" as defined by Applicants. In fact, DeLuca discloses nothing more than that its novel vitamin D glucuronide derivatives are water-soluble and lend themselves to intravenous and intramuscular formulations. As described in Applicants' specification (page 9, lines 13-14), the term "target molecule" or "targeting molecule" refers to "a molecule that binds to or influences metabolism of the tissue of interest." as recited in claim 59. As discussed in more detail below, glucuronide performs neither of these functions. In addition, glucuronide does not fall within the scope of the examples or equivalents thereof described in Applicants' specification, which is cited above. (See Applicants' specification, lines 14-27, page 9.) Simply put, glucuronide is not a target molecule moiety.

Nonetheless, the Examiner maintains that glucuronide has an affinity for plasma. Applicants respectfully request that the Examiner direct Applicants' attention to a specific portion of DeLuca in which glucuronide's affinity for plasma is specifically taught or suggested. Applicants have studied DeLuca in detail, and found no specific mention or reference to plasma

or blood whatsoever in the patent. Consequently, DeLuca does not teach or suggest that 25-hydroxy vitamin D₂ 25-D-glucuronic acid would somehow be directed to or have an affinity for plasma or any other tissue. Instead, DeLuca is directed to making vitamin D analogs and derivatives water-soluble. Generally, vitamin D analogs are not water soluble, and therefore, their application may be limited. By making these analogs water-soluble, "it lends itself to intravenous and intramuscular dosage formulations and to administration to patients who have difficulty in assimilating lipids." (DeLuca, col. 3, lines 65-68.) This, again, is much different than conjugating the vitamin D with a target molecule so that the target molecule targets and has an affinity for a particular tissue of interest (e.g., bone) as recited in Applicants' claimed invention. DeLuca's vitamin D compound derivatives are simply not "characterized by an ability for site-specific targeting of vitamin D compounds using conjugates of vitamin D and a targeting molecule having an affinity for a tissue of interest." (Applicants' specification, page 9, lines 3-5.)

More importantly, there is simply no specific motivation or suggestion in De Luca to modify or combine its teachings, particularly, with what is disclosed in Orme or Holick. Orme discloses an estradiol-tetracycline complex and that such complex could be "a bone seeking prodrug of estrogen in vivo." (Orme, p. 1377). Orme does not provide any explicit motivation or suggestion to modify or combine its estradiol-tetracycline compound with the vitamin D compounds disclosed in De Luca or Holick, or suggest or disclose that vitamin D compounds of DeLuca or Holick can be substituted for estradiol and reasonably provide the same results. The same applies to Holick.

Holick discloses, among other things, glycosylated, hydroxylated and fluorinated 1-thio vitamin D compounds that demonstrate biological activity and are water soluble. Holick discloses that vitamin D glycosides are hydrophilic and/or water soluble. Holick's compounds are vitamin D glycosides with the C₁ position occupied by a thio group, demonstrating that such substitution at the C₁ position maintains biological activity. Nowhere does Holick suggest that by glycosylating (or hydroxylating) and thio-substituting a vitamin D compound will the glycoside (or hydroxyl) or the thio group direct the vitamin D compound to a specific tissue such as bone or skin. The Examiner asserts that bone and skin have vitamin D receptors. Contrary to the Examiner's assertion, it is the targeting molecule that has the affinity for a specific tissue. Nowhere does Holick suggest or disclose that its modified portion (glycoside and thio) of a basic

vitamin D structure binds to vitamin D receptors. Applicants respectfully submit that the Examiner is improperly relying on hindsight in trying to establish a connection between these three references.

The Examiner asserts that it is *prima facie* obvious to combine two prior art compositions which are useful for the same purpose to form a third composition to be used for the same purpose. Orme discloses an estradiol complex for selective delivery of estrogen to bone. DeLuca and Holick disclose modifying vitamin D compounds to improve solubility. The prior art compositions are neither useful for the same purpose, nor would the idea of combining them logically flow from their teachings. There is absolutely nothing in DeLuca or Holick that suggests that its modified vitamin D compounds (or even unmodified vitamin D) can be linked to tetracycline to achieve their purpose of improved solubility while maintaining biological activity. Accordingly, Applicants respectfully submit that no suggestion or motivation exists in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine the teachings of all three references and to reasonably achieve Applicant's claimed invention.

Moreover, assuming *arguendo* that motivation exists to combine all three of these references, the Examiner still has not provided any reasoning as to why one of ordinary skill in the art would reasonably expect that De Luca's vitamin D compound could successfully be combined with Orme's estradiol compound using the teachings of Holick.

Moreover, even combined, the combination of the cited references still do not teach or suggest all the limitations of Applicants' claimed invention. More particularly, amended claim 44 recites a target molecule moiety comprising at least one of calcitonin, a bisphosphonate, a phosphate, polyaspartic acid, polyglutamic acid, an aminophosphosugar, osteonectin, bone sialoprotein, osteopontin, estrogen, dehydroepiandrosterone (DHEA), a metal ion-amino acid chelate, and combinations thereof. Nowhere in these references is any of these delineated target molecules taught or suggested. The Examiner contends that glucoronide and tetracycline are each target molecules. For the same and similar reasons as set forth above, Applicant respectfully submits that glucoronide is not a target molecule moiety. Tetracycline has been deleted from amended claim 44. Consequently, De Luca, Orme and Holick, taken separately or alone, do not teach or suggest the subject matter of independent claim 44.

As a result, a *prima facie* case of obviousness has not been established. Withdrawal of the 103 rejection and allowance of independent claim 44 and its dependent claims 2-6, 11, 17-18, 42, 47 and 49-53 are respectfully requested.

Dependent Claim 42

Dependent claim 42 depends from allowable independent claim 44, and is therefore allowable for the reasons set forth above. In addition, claim 44 is allowable because it specifies that the conjugate of claim 44 comprises at least one of 1 α -(OH)-24-aminoalkyl-1,1-bisphosphonate-D₂, 1-aminoalkyl-1,1-bisphosphonate-24-(OH)-D₂, 1 α ,24-(OH)₂-3-aminoalkyl-1,1-bisphosphonate-D₂, 1 α -aminoalkyl-1,1-bisphosphonate-25-(OH)-D₃, 1 α ,25-(OH)₂-3-aminoalkyl-1,1-bisphosphonate-D₃, 1 α -(OH)-25-aminoalkyl-1,1-bisphosphonate-D₃, and combinations thereof. In the Office action, the Examiner indicated that claim 42 is free of prior art. In view of the 112 rejections having been addressed, claim 42 is now in condition for allowance. During the interview, the Examiner indicated that addressing the 112 issues in the independent claim would make this dependent claim allowable.

Consequently, withdrawal of the rejections and allowance of dependent claim 42 are respectfully requested.

Dependent Claim 49

Dependent claim 49 depends from allowable independent claim 44, and is therefore allowable for the reasons set forth above. In addition, claim 49 is allowable because it further specifies that the target molecule moiety comprises at least one of calcitonin, a bisphosphonate, a phosphate, osteonectin, osteopontin, estrogen, and dehydroepiandrosterone (DHEA) and a combination thereof. During the interview, the Examiner explicitly stated that she would withdraw the 112 rejections with respect to these particular target molecule moieties.

Consequently, reconsideration and allowance of claim 49 are respectfully requested.

Independent Claim 20

Claim 20 stands rejected under 35 U.S.C. § 102(a) as being anticipated by Kobayashi. While Applicants believe that, in view of the accompanying Declaration, Kobayashi is not a proper prior art reference under §102(a), Applicants reiterate their arguments regarding

Kobayashi set forth in the response to the rejection to claim 44 hereinabove. Accordingly, Applicants respectfully submit that the §102 rejection is moot, and alternatively, the Kobayashi does not anticipate.

The Examiner also rejected claim 20 under 35 U.S.C. 103(a) as being unpatentable over Kobayashi et al. (*Analytical Biochemistry* 244: 374-383, Jan 1997; PTO 892) ("Kobayashi") or U.S. Patent No. 4,292,250 issued to DeLuca et al. ("DeLuca") each in view of Orme *et al.* (*Bioorg Med Chem Lett* 4: 1375-1380, 1994; PTO 892) ("Orme") and U.S. Patent No. 4,661,294 issued to Holick ("Holick").

Again, the §103 rejection using Kobayashi is moot because Kobayashi is not a proper prior art reference as evidenced by Applicants' declaration, and alternatively, as discussed hereinabove does not suggest Applicants' claimed invention as recited in claim 20.

Regarding the §103 rejection using the combination of De Luca, Orme and Holick, claim 20 is allowable for the same and similar reasons as set forth above with respect to claim 44. More particularly, claim 20 recites the conjugate as claimed 44, but used as a pharmaceutical composition. In other words, the pharmaceutical composition comprises the conjugate and a pharmaceutically acceptable carrier. Similar to claim 44, the Examiner has failed to establish a *prima facie* case of obviousness with respect to claim 20.

No motivation exists to combine De Luca, Orme and Holick as discussed above. Moreover, the Examiner has failed to provide reasons as to why one of ordinary skill in the art would reasonably expect the combination to succeed. Finally, the specific target molecules delineated in claim 20 have not been taught or suggested by De Luca, Orme and Holick, taken separately or alone.

As a result, a *prima facie* case of obviousness has not been established with respect to independent claim 20. Withdrawal of the 103 rejection and allowance of independent claim 20 and its dependent claims 22 and 55-58 are respectfully requested.

Dependent Claim 54

Dependent claim 54 depends from allowable claim 20, and is therefore allowable for the reasons set forth above. In addition, claim 54 is allowable for the reasons set forth above with respect to dependent claim 49. Consequently, withdrawal of the rejections and allowance of dependent claim 54 are respectfully requested.

Newly Added Independent Claim 59

Applicants note that none of the references used to reject the other independent claims, namely De Luca, Orme or Holick, teach or suggest, among other things, the vitamin D moiety defined in new independent claim 59. More particularly, the claimed vitamin D moiety specifies that R¹ is OH. In contrast, the corresponding R¹ group in De Luca is hydrogen. Holick's SR¹ corresponds to the claimed R¹, wherein Holick's R¹ is H, an acyl residue or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R¹ is an orthoester glycoside moiety.

Consequently, newly added independent claim 59 is allowable. Allowance of independent claim 59 and its dependent claims 60-64 is respectfully requested.

Dependent Claim 60

Dependent claim 60 depends from allowable claim 59, and is therefore allowable for the reasons set forth above. In addition, claim 60 is allowable for the reasons set forth above with respect claim 49. Allowance of dependent claim 60 is respectfully requested.

CONCLUSION

In view of the foregoing, reconsideration and allowance of the application are respectfully requested. Applicants again wish to thank the Examiner for the interview, and request an additional telephonic interview, if necessary, to place the application in condition for allowance. The Examiner is strongly encouraged to contact the undersigned by telephone should any other minor issues remain.

Respectfully submitted,



Teresa J. Welch
Reg. No. 33,049
Gregory J. Hartwig
Reg. No. 46,761

Docket No.: 017620-9277-00
Michael Best & Friedrich LLP
One South Pinckney Street
P. O. Box 1806
Madison, WI 53701-1806
(608) 257-3501

MARKED-UP VERSION OF ALL PENDING CLAIMS

2. (Amended Once) The conjugate of claim 44 [1], wherein the molar ratio of the at least one vitamin D moiety to the at least one target molecule moiety is 1:1.

3. (Amended Once) The conjugate of claim 44 [1], wherein the vitamin D moiety is associated with the target molecule moiety via a connecting group.

4. The conjugate of claim 3, wherein the connecting group is a linkage group formed by modification of the vitamin D moiety and the target molecule moiety to form a bond therebetween.

5. The conjugate of claim 3, wherein the connecting group is a bifunctional connector.

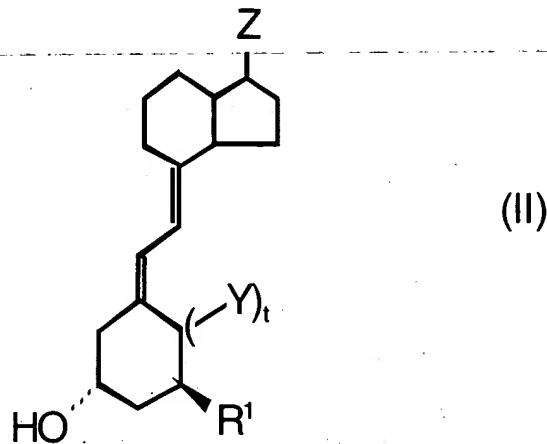
6. The conjugate of claim 3, wherein the vitamin D moiety is associated with the target molecule moiety via the connecting group and at least one additional connecting group.

11. The conjugate of claim 5, wherein the bifunctional connector is an amino acid chelated to the target molecule moiety and linked to the vitamin D moiety via an amide linkage.

17. (Amended Once) The conjugate of claim 44 [1], further comprising at least one therapeutic agent other than a vitamin D moiety conjugated therewith.

18. The conjugate of claim 17, wherein the therapeutic agent is a bone-therapeutic agent selected from the group consisting of conjugated estrogens or their equivalents, antiestrogens, calcitonin, bisphosphonates, calcium supplements, cobalamin, pertussis toxin, boron, dehydroepiandrosterone, transforming bone growth factor beta, activin, and bone morphogenic protein.

20. (Amended Once) A pharmaceutical composition comprising:
a conjugate which includes at least one vitamin D moiety having the formula



wherein R¹ is H or OH; Z represents a saturated or unsaturated, substituted or unsubstituted, straight-chain or branched C₁ - C₁₈ hydrocarbon group; Y is a =CH₂ group; and t is 0 or 1,

the vitamin D moiety being associated with at least one target molecule moiety having an affinity for a tissue of interest, the target molecule moiety comprising at least one of calcitonin, a bisphosphonate, a phosphate, polyaspartic acid, polyglutamic acid, an aminophosphosugar, osteonectin, bone sialoprotein, osteopontin estrogen, dehydroepiandrosterone (DHEA), a metal ion-amino acid chelate, and combinations thereof, and

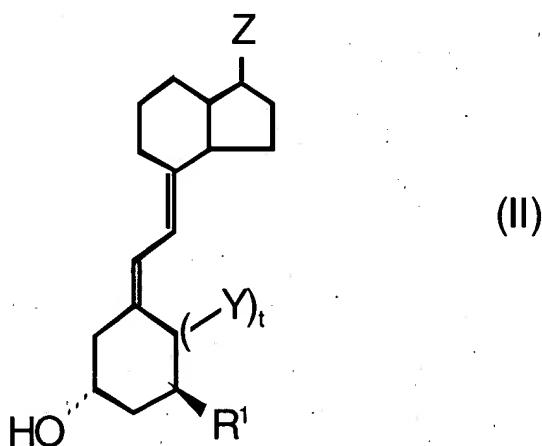
a suitable pharmaceutically acceptable carrier.

21. The pharmaceutical composition of claim 20, further comprising a differentially degradable coating encapsulating the conjugate for time release delivery of the conjugate.

22. The pharmaceutical composition of claim 21, wherein said coating is an enteric coating.

42. (Amended Once) The conjugate of claim 44, wherein the conjugate comprises [includes] at least one of 1α -(OH)-24-aminoalkyl-1,1-bisphosphonate-D₂, 1-aminoalkyl-1,1-bisphosphonate-24-(OH)-D₂, $1\alpha,24$ -(OH)₂-3-aminoalkyl-1,1-bisphosphonate-D₂, 1α -aminoalkyl-1,1-bisphosphonate-25-(OH)-D₃, $1\alpha,25$ -(OH)₂-3-aminoalkyl-1,1-bisphosphonate-D₃, 1α -(OH)-25-aminoalkyl-1,1-bisphosphonate-D₃, and combinations thereof.

44. (Amended Once) A conjugate comprising at least one vitamin D moiety having the formula



wherein R¹ is H or OH; Z represents a saturated or unsaturated, substituted or unsubstituted, straight-chain or branched C₁ - C₁₈ hydrocarbon group; Y is a =CH₂ group; and t is 0 or 1,

the vitamin D moiety being associated with a target molecule moiety having an affinity for a tissue of interest, the target molecule moiety comprising [including] at least one of [tetracycline,] calcitonin, a bisphosphonate, a phosphate, polyaspartic acid, polyglutamic acid, an aminophosphosugar, osteonectin, bone sialoprotein, osteopontin, [protein with bone mineral binding domains,] estrogen, [a steroid,] dehydroepiandrosterone (DHEA), a metal ion-amino acid chelate, [an antibody] and combinations thereof.

47. (Amended Once) The conjugate of claim 46, wherein said bisphosphonate is linked to said vitamin D moiety at a position on the vitamin D moiety which is C-1, C-3, C-24 or C-25.

49. (New) The conjugate of claim 44, wherein the target molecule moiety comprises at least one of calcitonin, a bisphosphonate, a phosphate, osteonectin, osteopontin, estrogen, and dehydroepiandrosterone (DHEA) and combinations thereof.

50. (New) The conjugate of claim 49, wherein the tissue of interest comprises at least one of bone, a malignancy site, and combination thereof.

51. (New) The conjugate of claim 50, wherein the tissue of interest comprises bone.

52. (New) The conjugate of claim 44, wherein the target molecule moiety comprises bisphosphonate.

53. (New) The conjugate of claim 44, wherein the tissue of interest comprises bone.

54. (New) The pharmaceutical composition of claim 20, wherein the target molecule moiety comprises at least one of calcitonin, a bisphosphonate, a phosphate, osteonectin, bone sialoprotein, osteopontin, estrogen, and dehydroepiandrosterone (DHEA) and combinations thereof.

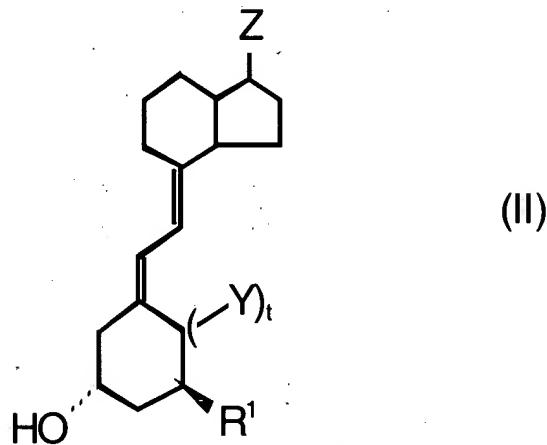
55. (New) The pharmaceutical composition of claim 54, wherein the tissue of interest comprises at least one of bone, a malignancy site, and combination thereof.

56. (New) The pharmaceutical composition of claim 55, wherein the tissue of interest comprises bone.

57. (New) The pharmaceutical composition of claim 20, wherein the target molecule moiety comprises bisphosphonate.

58. (New) The pharmaceutical composition of claim 20, wherein the tissue of interest comprises bone.

59. (New) A conjugate comprising at least one vitamin D moiety having the formula



wherein R¹ is OH; Z represents a saturated or unsaturated, substituted or unsubstituted, straight-chain or branched C₁ - C₁₈ hydrocarbon group; Y is a =CH₂ group; and t is 0 or 1,

the vitamin D moiety being associated with a target molecule moiety having an affinity for a tissue of interest, the target molecule moiety comprising at least one of tetracycline, calcitonin, a bisphosphonate, a phosphate, polyaspartic acid, polyglutamic acid, an aminophosphosugar, osteonectin, bone sialoprotein, osteopontin, estrogen, dehydroepiandrosterone (DHEA), a metal ion-amino acid chelate, and combinations thereof, the target molecule binding or influencing the metabolism of the tissue of interest.

60. (New) The conjugate of claim 59, wherein the target molecule moiety comprises at least one of calcitonin, a bisphosphonate, a phosphate, osteonectin, osteopontin, estrogen, and dehydroepiandrosterone (DHEA) and combinations thereof.

61. (New) The conjugate of claim 60, wherein the tissue of interest comprises at least one of bone, a malignancy site, and combination thereof.

62. (New) The conjugate of claim 61, wherein the tissue of interest comprises bone.

63. (New) The conjugate of claim 59, wherein the target molecule moiety comprises bisphosphonate.

64. (New) The conjugate of claim 58, wherein the tissue of interest comprises bone.